

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/003341

International filing date (day/month/year)
30.07.2004

Priority date (day/month/year)
30.07.2003

International Patent Classification (IPC) or both national classification and IPC
G01N33/533, A61K31/565

Applicant
AMERSHAM BIOSCIENCES UK LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/GB2004/003341

IAP20 Rec'd PCT/PTO 19 DEC 2005

Box No. I Basils of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/003341

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 16-25

because:

- ☒ the said international application, or the said claims Nos. 16-25 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. -
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/003341

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3,4,8-14
	No: Claims	1,2,5-7,15-27
Inventive step (IS)	Yes: Claims	14
	No: Claims	1-13,15-27
Industrial applicability (IA)	Yes: Claims	1-15,26,27
	No: Claims	16-25

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

IAP20 Rec'd PCT/PTO 19 DEC 2005
PCT/GB2004/003341

Re Item III.

Claims 16-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

V.1 Reference is made to the following documents:

- D1 : WO 03/020294 A (SCHMIDT, ALFRED; WIELAND, HEINRICH) 13 March 2003 (2003-03-13)
- D2 : STRESSER D M ET AL: "A HIGH-THROUGHPUT SCREEN TO IDENTIFY INHIBITORS OF AROMATASE (CYP19)" ANALYTICAL BIOCHEMISTRY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 284, no. 2, 2000, pages 427-430, XP000979096 ISSN: 0003-2697
- D3: WO 02/099424 A (AMERSHAM BIOSCIENCES UK LIMITED; SMITH, JOHN, ANTHONY; WEST, RICHARD,) 12 December 2002 (2002-12-12)

D1 discloses compounds having at least one detectable group and an inhibiting effect in relation to aromatase enzyme. It further relates to diagnostic and therapeutic methods using said compounds.

D2 concerns a fluorometric substrate for aromatase (O-benzylfluorescein benzyl ester) and its use in a screening method.

D3 discloses acridone derivatives and their use as fluorescent labels.

V.2 Novelty, inventive step and industrial applicability (Art. 33 PCT).

- 2.1 The present application concerns compounds containing a fluorescent dye molecule (R) coupled to a substrate for aromatase (S) via a linker (L) with the formula **R-L-S**, used for measuring aromatase activity in sample, diagnostic and screening methods.
- 2.2 The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claims 1, 2, 5-7, 15-27 is not new in the sense of Article 33(2) PCT in view of D1 or D2.

- 2.3 It is at present not apparent to which problem the compounds of **formula (I)** where **R** is an acridone dye or quinacridone (claims 3 and 4), where **L** is the linker as defined in claims 8 or 9, and where **S** is the substrate as given in claims 10-13, could be a solution. Acridone dye derivatives are known from D3 as fluorescence labels, the substrates defined by claims 10-13 are known from D2, and the linkers **L** as claimed in claims 8 or 9 are well known chemical linkers.

The subject matter of claims 3, 4 and 8-13 is therefore, not inventive.

- 2.4 The problem to be solved by claim 14 in view of the closest prior art document D2, can be seen as the provision of further labelled substrates for aromatase. The Applicant solves the problem by providing the compounds of **formula XX** where the label is an acridone dye molecule linked via a linker to testosterone.

The application differs from D1 in that the label is an acridone dye. All over D1 description's there are references to labelled aromatase substrates (also testosterone) detectable by spectroscopic methods, and imaging methods adapted to the detectable group. Nevertheless, this document is silent as to the use of acridone dyes conjugated to testosterone.

Although, document D3 discloses acridone florescent dyes and their use as fluorescent probes this document does not suggest acridone dyes bound to testosterone.

D2 concerns another substrate labelled with flourescein.

In view of the prior art documents D1-D3 it is not obvious to provide the compounds of **formula XX** where testosterone is labelled with an acridone dye. Therefore, claim 14 is inventive.

- 2.5 The subject matter of claims 1-15, 26 and 27 is industrial applicable.

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